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Haemodynamic effects of nifedipine and propranolol in patients with hypertrophic obstructive cardiomyopathy

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SUMMARY The haemodynamic effects of nifedipine, propranolol, and the combined administration of the two drugs were studied in 12 patients with hypertrophic obstructive cardiomyopathy. The combined administration of nifedipine and propranolol appeared to be superior to that of nifedipine alone. The spontaneous heart rate was reduced in most cases after nifedipine plus propranolol, and at atrial pacing the following results were obtained: left ventricular peak systolic pressure was reduced from 200±39 to 157±30 mmHg; a positive correlation was found between the pre-drug left ventricular end-diastolic pressure and the magnitude of reduction in left ventricular end-diastolic pressure; systolic blood pressure was reduced from 125±31 to 111±27 mmHg, and total peripheral resistance was reduced from 1403±307 to 1160±209 dyne s^{-1} cm^{-5}. The combined administration reduced the resting left ventricular outflow gradient from 76±19 to 45±26 mmHg, while cardiac index was left unchanged. The effects on mean pulmonary arteriolar resistance and mean pulmonary arteriolar and mean pulmonary capillary venous pressure were in most cases slight and insignificant. The results indicate an improved haemodynamic condition in patients with hypertrophic obstructive cardiomyopathy after the combined administration of nifedipine and propranolol: a treatment that might provide a new and useful alternative to already existing medication.

Drugs depresssing myocardial contractility should diminish the degree of left ventricular outflow obstruction in patients with hypertrophic obstructive cardiomyopathy,[1] and medical treatment of this disorder with beta adrenergic receptor blockers has been in use for many years. While propranolol reduces left ventricular outflow (LV-Ao) gradient at rest, on exercise, and during isoprenaline infusion,[2] and improves exercise performance,[3] and relieves the symptoms of angina pectoris,[4–6] the drug neither reduces the incidence of asymptomatic ventricular arrhythmias nor the risk of sudden death.[7–9] Calcium antagonists such as verapamil and nifedipine depress contractile force by inhibiting transmembrane calcium influx during excitation.[10–12] Hereditary hamster cardiomyopathy is thought to be the result of a membrane disease, and abnormal calcium flux probably plays a prominent role in its pathogenesis.[13] The possible relation between this cardiomyopathy and hypertrophic obstructive cardiomyopathy has been discussed.[14] It has been shown that calcium antagonistic drugs, and, to a lesser extent, beta adrenergic receptor blockers are able to prevent the development of heart lesions in hamsters with hereditary cardiomyopathy.[13] Recently, it has been reported that the calcium antagonistic drug verapamil reduces the resting left ventricular outflow gradient, increases the heart rate and cardiac output, and lowers systolic blood pressure in patients with hypertrophic obstructive cardiomyopathy.[15] With long term treatment by this drug exercise tolerance increased, and heart size, QRS complex amplitude, left ventricular outflow gradient, free wall thickness, and left ventricular diameter were reduced.[16 17] The conclusion drawn from one of these studies was that verapamil is superior to beta blockers in hypertrophic obstructive cardiomyopathy.[16]

By reducing the entry of calcium ions into smooth muscle cells, calcium antagonists reduce blood pressure and total peripheral resistance, thereby inducing a reflex sympathetic stimulation of the heart.[18–20] This effect, which is presumed to be present even during chronic administration of nifedipine,[21 22] will probably, to a certain extent, counteract the negative inotropic action of the drugs.[23] A more rational way to treat patients with hypertrophic obstructive car-

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diomyopathy would be to combine a calcium antagonist with a beta adrenergic receptor blocker. Verapamil increases atrioventricular nodal conduction time and refractoriness,[24] and a pronounced and dose related increase in PR interval after this drug has been found in patients with hypertrophic obstructive cardiomyopathy.[15] In addition, sinus arrest and sinus bradycardia associated with oral verapamil treatment have been described in 2% and 11% of these patients, respectively.[25] Because of the tendency to produce atrioventricular block, the combined administration of verapamil and a beta blocker is not recommended.[26 27] On the other hand, nifedipine alone[28 29] or in combination with a beta adrenergic receptor blocker has no detrimental effect on atrioventricular nodal function.[19 30] This paper describes the acute haemodynamic changes in patients with hypertrophic obstructive cardiomyopathy induced by nifedipine, propranolol, and the combination of nifedipine and propranolol.

Patients and haemodynamic measurements

Twelve patients, six men and six women, aged 26 to 67 years (mean 45 years) participated in the study. Before catheterisation a tentative diagnosis of hypertrophic obstructive cardiomyopathy was made on the basis of symptoms, physical examination, and electrocardiographic and echocardiographic abnormalities. The patients were all in normal sinus rhythm. Informed consent was obtained from all. All cardiac medication was discontinued at least three days before catheterisation.

The investigation was carried out with the patients supine and fasted. They were premedicated with 0·1 g aprobarbitone. Right heart catheterisation was performed with a Swan-Ganz thermodilution catheter advanced to the pulmonary artery, and a pacemaker electrode was placed in the right atrium. Cardiac output was measured at least in duplicate by thermodilution. Mean pulmonary arteriolar ($\overline{PA}$) and mean pulmonary capillary venous pressure ($\overline{PCV}$) were obtained by electrical integration recorded on a Mingograph 82 (Elema-Schönander, Stockholm, Sweden). Left ventricular peak systolic pressure (LVPSP) and left ventricular end-diastolic pressure (LVEDP) were obtained through an end-hole catheter (multipurpose side-holes, F. 8, Ducor) placed in the apex of the left ventricle by the retrograde femoral technique. The left ventricular-aortic pressure (LV-Ao) gradient was measured by slowly withdrawing the catheter from the apex of the ventricle to the aortic root. Particular care was taken in order to avoid its entrapment. Changes in heart rate induced by exercise, isoprenaline infusion, and atrial pacing may change the left ventricular outflow gradient and left ventricular end-diastolic pressure in patients with hypertrophic obstructive cardiomyopathy[2 31] and, in order to eliminate rate dependent haemodynamic changes, all recordings were performed at an atrial pacing rate about 20 beats above the heart rate in the control period. The patients were then randomised into two groups.

Patients in group 1 were first given nifedipine 20 mg to chew in the mouth and the recordings were repeated 30 minutes later. Propranolol, 5 mg intravenously over five minutes, was then given, and the measurements were repeated 10 minutes after the end of the injection.

Patients in group 2 were given the propranolol first, 5 mg intravenously with measurements 10 minutes later, and then the 20 mg of nifedipine to chew with repeat measurements 30 minutes later.

CALCULATIONS AND STATISTICAL ANALYSIS

Pulmonary arteriolar resistance

$$(PAR)=\frac{\overline{PA}-\overline{PCV}}{CO}\times 80 \text{ dyne s}^{-1} \text{ cm}^{-5}$$

Mean aortic pressure ($\overline{Ao}$)$=\frac{\text{systolic BP}+2\times\text{diastole BP (mmHg)}}{3}$

Total peripheral resistance (TPR)$=\frac{Ao}{CO}\times 80 \text{ dynes}^{-1} \text{ cm}^{-5}$

Cardiac index (CI)$=\frac{CO \text{ (l/min)}}{\text{Total body surface (m}^2\text{)}}$

The results are expressed as mean±SD. Student's t test for paired comparison was used when observations before were compared with those after the drugs. Differences were regarded as significant when $p\leqq 0{\cdot}05$.

Results

The spontaneous heart rate for the whole group of patients in the control period was 76±14 beats/minutes (Table 1). Neither nifedipine, propranolol, nor the combined administration of the two drugs significantly changed mean heart rate (Table 1). While nifedipine alone, however, tended to increase heart rate, propranolol and the combined administration tended to decrease it (Table 1).

With atrial pacing, nifedipine and propranolol lowered left ventricular peak systolic pressure in most cases, and the combined administration of the two drugs significantly reduced left ventricular peak systolic pressure for the whole group of patients from 200±39 to 157±30 mmHg ($p<0{\cdot}001$) (Table 1, Fig. 1).

Eight out of 12 patients had a left ventricular end-diastolic pressure in the control period above the normal limit (>12 mmHg). Neither the separate administration of nifedipine, propranolol, nor the

Table 1 *Haemodynamic measurements in control period (C), after nifedipine (N), propranolol (P), and the combined administration of nifedipine and propranolol (N+P, P+N)*

	C_1 (6 patients)		N		$N+P$	C_2 (6 patients)		P		$P+N$	C_1+C_2 (12 patients)		$N+P$
Heart rate (beats/min)	73	NS	81	*	66	79	NS	70	NS	70	76	NS	68
	(18)		(16)		(6)	(9)		(13)		(10)	(14)		(8)
LVPSP (mmHg)	197	**	180	NS	153	203	NS	179	NS	161	200	***	157
	(55)		(61)		(37)	(19)		(36)		(44)	(39)		(30)
LVEDP (mmHg)	17	NS	17	NS	12	17	NS	15	*	17	17	NS	15
	(10)		(6)		(3)	(4)		(5)		(2)	(7)		(4)
SBP (mmHg)	127	NS	123	NS	112	123	NS	122	*	108	125	*	111
	(40)		(48)		(32)	(21)		(19)		(23)	(31)		(27)
TPR (dyne s^{-1} cm^{-5})	1413	**	1050	**	1138	1393	NS	1598	**	1182	1403	**	1160
	(310)		(217)		(252)	(333)		(276)		(179)	(307)		(209)
LV-Ao gradient (mmHg)	70	NS	54	NS	38	81	*	57	NS	52	76	***	45
	(17)		(35)		(23)	(22)		(30)		(30)	(19)		(26)

Asterisks indicate those values that are significantly different (*p<0·05; **p<0·01; ***p<0·001); NS, not significant. SD in parentheses. LVPSP, left ventricular peak systolic pressure; LVEDP, left ventricular end-diastolic pressure; SBP, systolic blood pressure; TPR, total peripheral resistance; LV-Ao, left ventricular outflow.

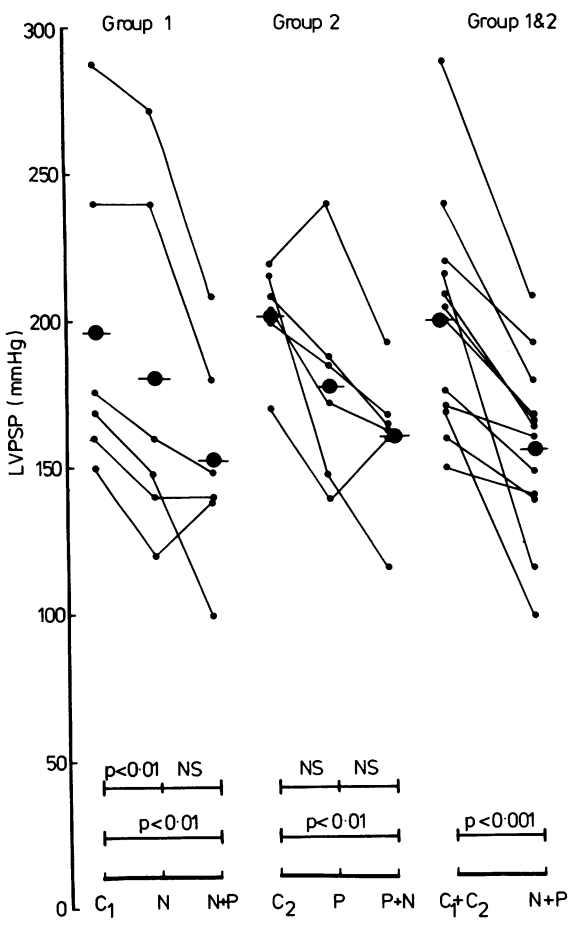

Fig. 1 *Effect of nifedipine (N) and propranolol (P) on left ventricular peak systolic pressure (LVPSP). NS, not significant.*

combined administration of the two drugs significantly changed it (Table 1, Fig. 2); after the combined administration of nifedipine and propranolol, however, the fall in left ventricular end-diastolic pressure (△ LVEDP) was significantly correlated to the pre-drug values (Fig. 3). In the group of six patients initially given nifedipine, the only patient with a very high left ventricular end-diastolic pressure had the filling pressure definitely reduced; in the remaining five patients in whom it was normal or slightly raised, the values were essentially unchanged after the drug was given (Fig. 3).

Systolic blood pressure did not change after the initial administration of nifedipine (Table 1, Fig. 4). Intravenous injection of propranolol to patients not pretreated with nifedipine did not reduce systolic blood pressure (Table 1). The combined administration of the two drugs, however, significantly reduced systolic blood pressure for the whole group (p<0·05) (Table 1, Fig. 4). Nifedipine reduced total peripheral resistance in all patients, propranolol increased it in most patients; the combined administration, on the other hand, reduced it in all but one, and to a significant degree (p<0·01) (Table 1, Fig. 5).

The pretreatment resting left ventricular outflow gradient was 76±19 mmHg (range 50 to 114 mmHg) (Table 1). While the separate administration of nifedipine or propranolol reduced the gradient in the majority of patients, the reducing effect of the combined administration was much more significant (Table 1, Fig. 6). In one patient, the gradient increased after the initial administration of nifedipine (from 96 to 120 mmHg), with a simultaneous reduction in systolic blood pressure from 144 to 120 mmHg; after the combined administration, on the other hand, the gradient fell to 80 mmHg (Fig. 6).

Whereas nifedipine significantly increased cardiac index, propranolol reduced it in most cases; the com-

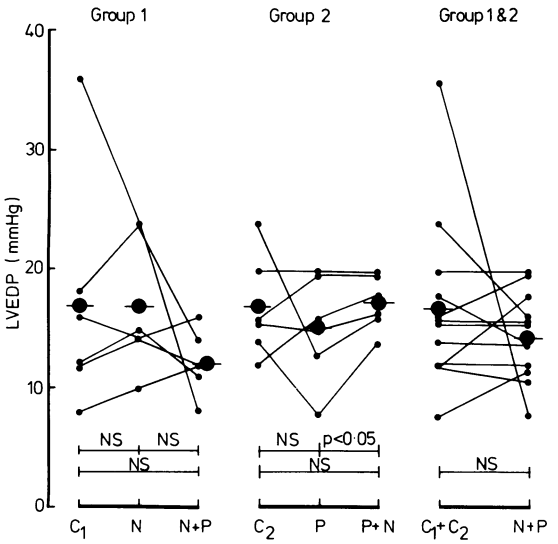

Fig. 2 *Effect of nifedipine (N) and propranolol (P) on left ventricular end-diastolic pressure (LVEDP). NS, not significant.*

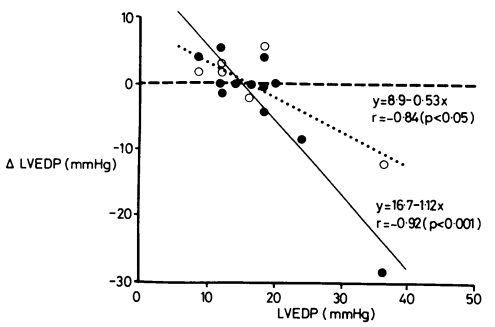

Fig. 3 *Relation between control left ventricular end-diastolic pressure (LVEDP) and change in LVEDP (△ LVEDP) after nifedipine (open circles, interrupted line), and the combined treatment with nifedipine and propranolol (closed circles, solid line).*

bined administration caused a slight and statistically insignificant increase (Table 2, Fig. 7). The individual increases or decreases in cardiac index induced by the separate or combined administration of the drugs were, with few exceptions, associated with a fall or an increase in total peripheral resistance, respectively (Fig. 8).

Mean pulmonary arteriolar pressure was slightly but significantly increased by the combined administration of nifedipine and propranolol (Table 2). Neither nifedipine, propranolol, nor the combined administration of the two drugs significantly changed mean pulmonary arteriolar resistance and mean pulmonary capillary venous pressure (Table 2).

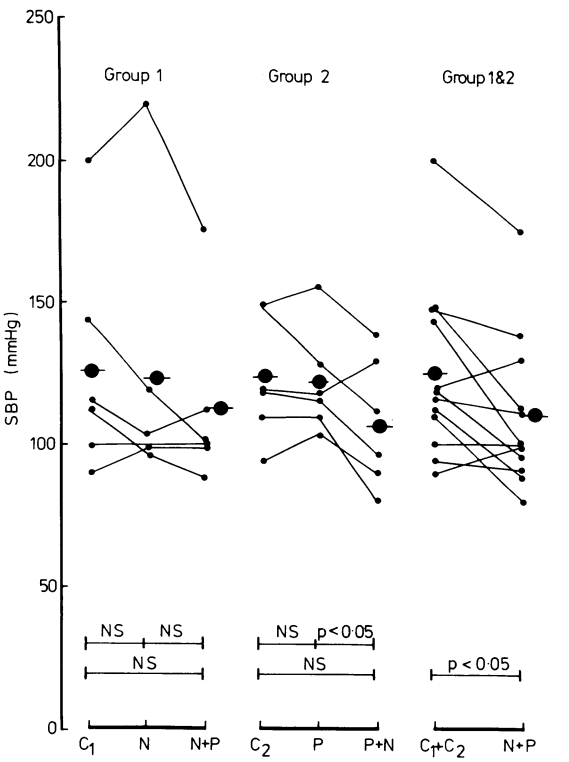

Fig. 4 *Effect of nifedipine (N) and propranolol (P) on systolic blood pressure (SBP). Symbols as in Fig. 2.*

The PR interval on the surface electrocardiogram was neither changed by nifedipine, propranolol, nor by the combined administration of the two drugs.

Discussion

The increase in heart rate induced by nifedipine in most of our patients is caused by a baroreceptor mediated activation of the sympathetic tone,[20 32] an effect that could be completely blocked by intravenous administration of propranolol.

The fall in left ventricular peak systolic pressure after nifedipine is in accordance with previous reports.[23 33 34] This fall was more pronounced when the drug was combined with propranolol. The hypercontractile state in hypertrophic obstructive cardiomyopathy has been related to myocardial calcium overload,[8 15 16] resulting from an abnormality of the cell membrane[8] and/or an increased and abnormal sensitivity to catecholamines,[35] which in that way augments calcium influx.[36–38]

The majority of the patients had raised left ventricular end-diastolic pressures, consistent with earlier reports on patients with hypertrophic obstructive cardiomyopathy.[31] Prolonged left ventricular isovolumic

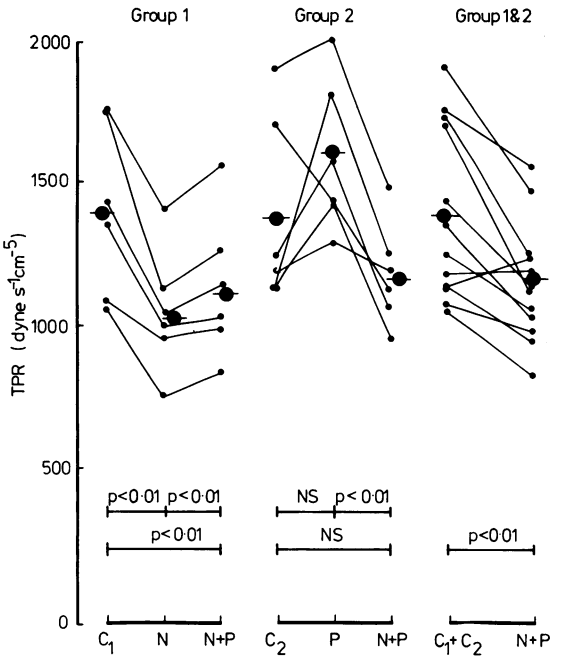

Fig. 5 *Effect of nifedipine (N) and propranolol (P) on total peripheral resistance (TPR). Symbols as in Fig. 1.*

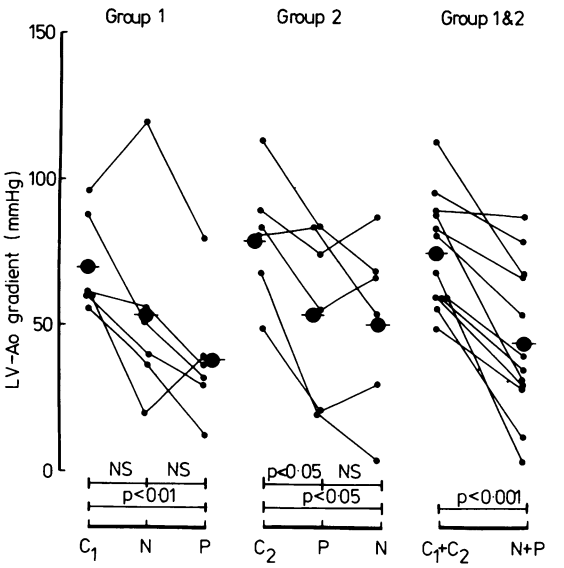

Fig. 6 *Effect of nifedipine (N) and propranolol (P) on resting left ventricular outflow (LV-Ao) gradient. Symbols as in Fig. 1 and 2.*

relaxation time, together with an impaired diastolic filling, have also been shown in patients with this malady.[39 40] It has been suggested that the raised left ventricular end-diastolic pressure not only reflects the severity of the disease, but is the main determinant of symptoms and prognosis.[41] While isoprenaline lowers left ventricular end-diastolic pressure in normal individuals as well as in patients with heart disease other than hypertrophic obstructive cardiomyopathy,[42] it has been shown that left ventricular end-diastolic pressure increases after isoprenaline in most patients with that disease.[31] In addition, the administration of isoprenaline to patients with hypertrophic obstructive cardiomyopathy always increases the obstruction to left ventricular outflow and muscular exercise often increases it.[1 2] Our results indicate that nifedipine alone, and in particular the combined administration of nifedipine and propranolol, may improve left ventricular filling and compliance in those patients with increased left ventricular end-diastolic pressure. Recently it has been reported that left ventricular isovolumic relaxation time in hypertrophic obstructive cardiomyopathy was favourably shortened by the administration of nifedipine, 10 to 20 mg sublingually.[43] Though left-sided filling pressure rose after verapamil in a number of patients with hypertrophic obstructive cardiomyopathy, this phenomenon occurred mainly in patients who had normal pressures in the control period.[15]

The effects of nifedipine and the combined administration of nifedipine and propranolol on systolic blood pressure and total peripheral resistance are in accordance with previous observations.[20 32 44]

The effects of nifedipine and propranolol and the combination of the two drugs on mean pulmonary arteriolar resistance and mean pulmonary arteriolar and mean pulmonary capillary venous pressure were in most cases slight and insignificant.

Whereas the separate administration of nifedipine and propranolol reduced left ventricular outflow gradient in most patients, the combined administration of the two drugs caused a more pronounced and general reduction in the gradient in all patients. Any changes in the gradient result from alterations in left ventricular peak systolic pressure and systolic blood pressure. It has been suggested that reduction in systolic blood pressure and total peripheral resistance may increase the left ventricular outflow gradient in patients with hypertrophic obstructive cardiomyopathy,[45] and in one patient this was found after nifedipine. The combined administration, however, reduced the gradient slightly in comparison with the control value.

The nifedipine-induced increase in cardiac index during atrial pacing found in our study is consistent with a previous report.[32] Even in combination with propranolol, which by itself reduces cardiac index,[2] eight out of 12 patients were able to increase their cardiac index in relation to the control values. As heart rate was kept constant by atrial pacing, it is

Table 2 *Haemodynamic measurements in control period (C), after nifedipine (N), propranolol (P), and combined administration of nifedipine and propranolol (N+P, P+N)*

	C_1 (6 patients)		N		$N+P$	C_2 (6 patients)		P		$P+N$	C_1+C_2 (12 patients)		$N+P$
CI (l/min per m²)	3·0 (0·5)	**	3·5 (0·5)	**	3·3 (0·5)	3·1 (0·3)	NS	2·8 (0·7)	**	3·2 (0·5)	3·0 (0·3)	NS	3·2 (0·3)
$\overline{PA}$ (mmHg)	19 (7)	NS	21 (9)	NS	21 (10)	15 (6)	NS	16 (6)	*	19 (6)	17 (7)	*	20 (8)
$\overline{PCV}$ (mmHg)	12 (6)	NS	15 (8)	NS	14 (8)	10 (5)	NS	11 (4)	NS	12 (5)	11 (6)	NS	13 (7)
PAR (dyne s^{-1} cm^{-5})	102 (64)	NS	80 (29)	NS	102 (53)	82 (30)	NS	102 (42)	NS	87 (30)	92 (49)	NS	95 (42)

Asterisks indicate those values that are significantly different (*p<0·05; **p<0·01); NS, not significant. SD in parentheses. CI, cardiac index; PA, mean pulmonary arteriolar pressure; PCV, mean pulmonary capillary venous pressure; PAR, pulmonary arteriolar resistance.

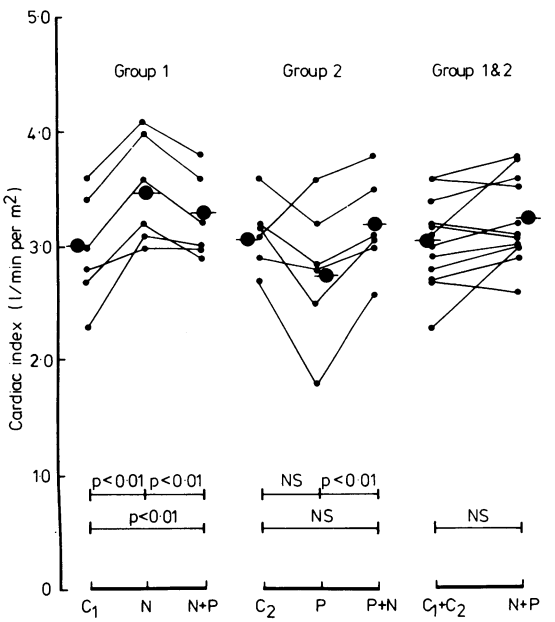

Fig. 7 *Effect of nifedipine (N) and propranolol (P) on cardiac index. Symbols as in Fig. 1.*

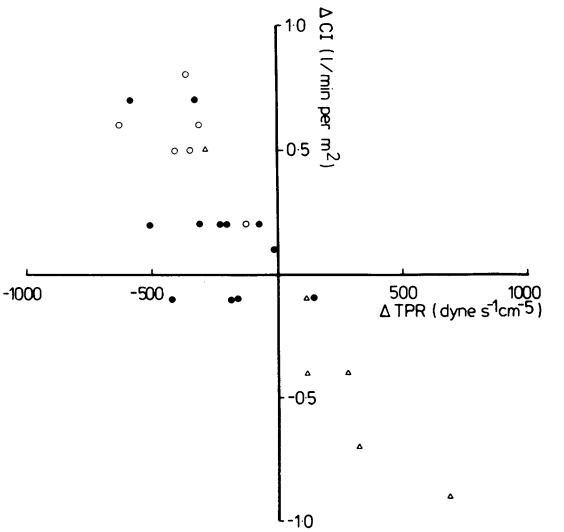

Fig. 8 *Relation between the changes in total peripheral resistance (△ TPR) and cardiac index (△ CI) after nifedipine (open circles), propranolol (open triangles), and the combined administration of nifedipine and propranolol (closed circles).*

probable that the increase in cardiac index observed in all patients after nifedipine and in most patients after the combined administration of both drugs was mainly the result of a reduction in total peripheral resistance (afterload). Even in the patient where the left ventricular outflow gradient increased after nifedipine, a rise of cardiac index from 3·0 to 3·6 l/min per m² was found.

The lowering of left ventricular peak systolic pressure, systolic blood pressure, and left ventricular outflow gradient in the presence of a maintained cardiac index will reduce myocardial oxygen needs and have a favourable effect on the balance between myocardial oxygen supply and demand and also prevent the vicious cycle of obstruction hypertrophy.[2] In this acute haemodynamic study, the combined administration of nifedipine and propranolol appeared to be superior to the separate administration of nifedipine, and the increased sympathetic tone secondary to nifedipine seemed to be well counteracted by beta adrenergic receptor blockade. The combined effects on left ventricular peak systolic pressure, systolic blood pressure, and left ventricular outflow gradients were more pronounced, cardiac index was in most patients maintained at higher levels than in the control period, total peripheral resistance was reduced, and left ventricular end-diastolic pressure was decreased in those patients having high control values. Since an extension of the study would be time consuming and also troublesome to the patients, drug-induced haemodynamic changes were not measured at a spontaneous heart rate. The negative chronotropic

action of the combined administration of nifedipine and propranolol will have a favourable effect on myocardial oxygen consumption.[46] No side effects were observed, and no disturbance in atrioventricular nodal function was noted.

Our results indicate that the combined administration of nifedipine and propranolol in hypertrophic obstructive cardiomyopathy provides a new alternative to already existing treatment.

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